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## Effects of Exercise and Stress Management Training on Nighttime Blood Pressure Dipping in Patients with Coronary Heart Disease: A Randomized Controlled Trial

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### Abstract

**INTRODUCTION**—Blunted nighttime blood pressure (BP) dipping is prognostic of cardiovascular morbidity and mortality. Patients with coronary heart disease (CHD) are often characterized by a blunted nighttime BP dipping pattern. The present study compared the effects of two behavioral intervention programs, aerobic exercise (EX) and stress management (SM) training, with a usual care (UC) control group on BP dipping in a sample of CHD patients.

**METHODS**—This was a secondary analysis of a randomized controlled trial with allocation concealment and blinded outcome assessment in 134 patients with stable CHD and exercise-induced myocardial ischemia. Nighttime BP dipping was assessed by 24-hour ambulatory blood pressure monitoring (ABPM), at pre-randomization baseline and following 16 weeks of one of the following treatments: usual medical care; usual care plus supervised aerobic exercise for 35 min 3 times per week; usual care plus weekly 1.5 hr sessions of stress management training.

**RESULTS**—The EX and SM groups exhibited greater improvements in SBP dipping ( $P = .052$ ) and DBP dipping ( $P = .031$ ) compared with UC. Post intervention SBP percent-dipping means were 12.9 (SE = 1.5) for SM, 11.1 (SE = 1.4) for EX, and 8.6 (SE = 1.4) for UC. Post intervention DBP percent-dipping means were 13.3 (SE = 1.9) for SM, 14.1 (SE = 1.8) for EX, and 8.8 (1.8) for UC.

**CONCLUSIONS**—For patients with stable CHD, exercise or stress management training resulted in improved nighttime BP dipping compared to usual medical care. These favorable effects of healthy lifestyle modifications may help reduce the risk of adverse clinical events.

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## Keywords

Ambulatory blood pressure monitoring; blood pressure dipping; coronary heart disease; stress management; exercise

## INTRODUCTION

Blunted nighttime blood pressure (BP) dipping, typically defined as <10% fall in average BP from daytime to nighttime, is a strong prognostic indicator of cardiovascular morbidity and mortality for both hypertensive and non-hypertensive individuals<sup>1-4</sup>. Blunted nighttime BP dipping also appears to be unusually common in patients with coronary heart disease (CHD), with a non-dipping pattern approximately twice as common as in age-matched controls.<sup>5-7</sup> For vulnerable CHD patients, blunted nighttime BP dipping may exacerbate their heightened risk of adverse cardiovascular disease (CVD) events. As a result, there have been a number of different approaches designed to enhance BP dipping in various CVD populations.

Chronotherapy is one successful approach to enhancing nighttime BP dipping. For patients with hypertension, bedtime dosing of antihypertensive medications, rather than typical morning dosing, lowers nighttime BP<sup>8-10</sup>. Nighttime dosing of melatonin, a hormone involved in diurnal regulation, also may enhance BP dipping through multiple physiological pathways<sup>11</sup>. Lifestyle factors including physical activity and psychological stress also affect the nocturnal decline in BP. For example, greater daytime physical activity has been related to enhanced nighttime BP dipping<sup>12</sup>, but the evidence is equivocal with regard to whether dipping is improved with exercise training<sup>13-16</sup>. Psychological stress also has been linked to a blunted fall in nighttime BP<sup>17</sup>, suggesting that behavioral interventions designed to reduce stress may also enhance dipping. However, to our knowledge, no study to date has evaluated whether stress reduction may improve BP dipping in CHD patients. The present report from the Smart Heart trial<sup>18</sup> examined the effects of a 16-week stress management (SM) intervention and aerobic exercise (EX) compared to Usual Care (UC) on nighttime BP dipping in patients with CHD. The primary results of the trial, which showed that both active interventions improved biomarkers of cardiovascular risk, have been reported previously.<sup>18</sup> To assess BP dipping, 24-hour ABPM was performed before and after the interventions. We hypothesized that both EX and SM would result in enhanced nighttime BP dipping compared to UC.

## METHODS

### Study Design

This is a secondary analysis of the Smart Heart trial of 134 patients with CHD and exercise-induced myocardial ischemia. Primary outcomes, including stress-induced myocardial ischemia, CVD biomarkers, and measures of general distress have been reported previously.<sup>19</sup> This report focuses on 24-hour ABPM data that have not been reported previously. The study was conducted from January 199 through February 2003. The study was supported by grants HL59672 and M01-RR-30 from the National Institutes of Health.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

## Participants

The patient sample consisted of 134 patients (92 male; 42 female), age 40–84 years (mean age  $62 \pm 10$  years), with documented CHD, and evidence of exercise-induced myocardial ischemia. This study was approved by the Institutional Review Board at Duke University Medical Center and written informed consent was obtained from all participants prior to their participation.

## Procedures

**24-Hour Ambulatory Blood Pressure Monitoring**—ABPM was conducted during a typical workday. The AccuTracker II ABP Monitor (Suntech, Raleigh, NC) was worn for approximately 24 hours, usually starting between 8:00 AM and 10:00 AM until the same time the following morning. The AccuTracker II, which measures BP noninvasively based on the auscultatory technique, has been validated for accuracy.<sup>20–22</sup> It was programmed to take 3 BP measurements per hour at random intervals during daytime hours, and 2 readings per hour during the participant's anticipated nighttime sleep period. Participants were instructed to follow their normal daily schedule. Mean SBP and DBP values were computed based on all valid readings obtained during waking hours and during nighttime sleep (defined by the participants' retrospective reports of when they turned out room lights at bedtime to the time they got out of bed the following morning). SBP and DBP dipping were computed as continuous variables, defined as percent change from mean waking BP to mean nighttime sleep BP.

**Medications**—Because the focus of the parent trial<sup>18</sup> was on mental stress-induced myocardial ischemia, unless medically contraindicated, patients discontinued their use of anti-ischemic medications, including beta-blockers, calcium channel blockers, and long-lasting nitrates for 48 hours prior to their baseline and post-intervention ABPM assessments. Twenty-eight participants could not safely discontinue their anti-ischemic medications, and those that did discontinue them did so for 3 days. Most participants were taking a daily low-dose aspirin and lipid lowering drugs. There were no group differences in medication usage, which was described in detail in the primary publication.<sup>18</sup>

**Interventions**—Once patients completed their baseline ABPM assessments, they resumed their usual medical management on anti-ischemic medications. Importantly, participants were taking the same medications for their baseline and post-intervention 24-hour ABPM study. Using block randomization, patients were randomly assigned to one of three treatment conditions.

**Exercise training (EX):** Patients assigned to the aerobic exercise condition exercised 3 times per week for 16 consecutive weeks. Exercise sessions consisted of a 10 minute warm up period involving stretching and exercise on a stationary bicycle at a heart rate of 50–70% heart rate reserve followed by 35 minutes of walking and jogging at a target intensity of 70–85% heart rate reserve.

**Stress Management training (SM):** The SM training program was based upon our prior work<sup>23</sup>, which emphasizes a cognitive-social learning model of behavior. The interaction of the social environment with personality traits that predispose individuals to respond to situations in particular ways was highlighted, and the treatment program was based upon the notion that emotion and behavior are largely determined by individuals' cognitive perceptions. The program consisted of 16 weekly 1.5 hour sessions conducted in a group setting with 6–8 patients per group. Three key components of the intervention included education, coping skills training, and social support. Participants were provided information about CHD, the structure and function of the heart, traditional risk factors, and emotional stress. Stress was considered to be an imbalance between excessive demands and inadequate coping skills. The coping skills training aspect of the intervention included instruction in specific skills to reduce the affective, behavioral, cognitive, and physiologic components of stress. Therapeutic techniques included graded task assignments, monitoring irrational automatic thoughts, and generating alternative interpretations of situations or unrealistic thought patterns. Patients were instructed in progressive muscle relaxation and imagery techniques, along with training in assertiveness, problem solving, and time management. Role playing also was utilized. Finally, group interaction and social support were encouraged.

**Usual Care (UC):** Patients in the UC condition were monitored on a monthly basis to ensure that they had not joined any exercise or stress management training program. Patients were maintained on their regular medical regimens and saw their local cardiologists as needed. No attempt was made to in any way to alter the usual care that these patients received from their personal physicians.

### Statistical Analysis

Treatment group effects for BP dipping were evaluated using general linear models through SAS 9.2 (PROC GLM, SAS Institute, Cary, NC). All models included pre-randomization baseline values of the outcome variable, gender, and ethnicity. Analyses of treatment effects followed the intention-to-treat (ITT) principle, with post-treatment missing data managed using Markov chain Monte Carlo multiple imputation methods available in SAS (PROC MI) and 1000 imputations. Planned, orthogonal contrasts were conducted comparing 1) both active treatment groups (EX and SM) vs. UC and 2) the EX and SM groups. We evaluated the extent to which models met assumptions, including additivity, linearity, and distribution of residuals. We found no evidence of significant violations of these assumptions.

## RESULTS

One hundred and thirty-four individuals were randomized to participate in the intervention including 44 to SM, 48 to EX, and 42 to UC, as previously reported (Table 1).<sup>18</sup> The flow of participants from recruitment through post-intervention assessments is illustrated in Figure 1.

We did not observe any baseline imbalance in daytime or nighttime ambulatory BPs (all  $p$ 's > .774), SBP dipping ( $P = .853$ ), or DBP dipping ( $P = .951$ ). At baseline, 124 participants

provided BP dipping data. Of these 64 (52%) were considered ‘dippers’ (  $\geq 10\%$  mean SBP dip from daytime to nighttime).

### Nocturnal Blood Pressure Dipping Changes

Examination of planned treatment contrasts demonstrated that the EX and SM groups exhibited a strong trend towards greater improvements in SBP dipping compared with the UC condition ( $P = .052$ ). SBP dipping improvements from pre-to post-treatment were 3.2 (SE = 1.5) % for SM, 1.7 (SE = 1.5) % for EX, and  $-0.7$  (SE = 1.4) % for UC (Table 2). As shown in Figure 2, this corresponded to mean post-treatment SBP dipping values of 12.9 (SE = 1.5) % for SM, 11.1 (SE = 1.4) % for EX, and 8.6 (1.4) % for UC.

Examination of changes in DBP dipping demonstrated a similar pattern of findings, with the treatment groups demonstrating greater improvements in DBP dipping compared with the UC condition ( $P = .031$ ). DBP dipping improvements from pre-to post-treatment were 1.2 (SE = 1.9) % for SM, 2.5 (SE = 1.9) % for EX, and  $-3.0$  (SE = 1.8) % for UC, corresponding to mean post-treatment DBP dipping values of 13.2 (SE = 1.9) % for SM, 14.0 (SE = 1.9) % for EX, and 8.8 (1.8) % for UC (Figure 2; Table 2).

### Daytime Blood Pressure Changes

Examination of average daytime SBP revealed no overall change from baseline to post-intervention ( $P = .272$ ), and treatment groups did not differ following the interventions ( $P = .673$ ), with post-treatment values of 131.1 (1.7) mm Hg for SM, 130.5 (1.7) mm Hg for EX, and 130.1 (1.6) mm Hg for UC. A similar non-significant pattern was noted for DBP ( $P = .887$ ), with post-treatment daytime DBP values of 74.6 (1.0) mm Hg for SM, 73.9 (0.9) mm Hg for EX, and 74.6 (0.9) mm Hg for UC (Table 2).

### Nighttime Blood Pressure Changes

Examination of mean nighttime SBP revealed that treatment groups did not differ significantly following treatment ( $P = .305$ ), with post-treatment nighttime SBP values of 114.2 (2.4) mm Hg for SM, 116.1 (2.3) mm Hg for EX, and 118.8 (2.3) mm Hg for UC. In contrast, nighttime DBP values were lower in the treatment groups compared with UC controls ( $P = .038$ ), with values of 64.6 (1.6) mm Hg for SM, 63.5 (1.5) mm Hg for EX, and 68.0 (1.5) mm Hg for UC (Table 2).

## DISCUSSION

Few studies have examined nighttime BP dipping in patients with CHD. Mousa and colleagues first described this phenomenon in a study of 68 men with documented CHD who exhibited a significantly blunted nighttime BP dipping compared to 68 age-matched healthy men.<sup>5</sup> Our prior work described similar findings in a study comparing 54 postmenopausal women with documented CHD with 48 age-matched control women.<sup>6</sup> Most recently, in a study of 401 patients with CVD, including those with CHD and others who had experienced an ischemic stroke, Cai et al. reported that blunted nighttime BP dipping was related to greater risk of a cardiovascular event.<sup>7</sup> The present study provides further evidence that patients with CHD are prone to exhibit a non-dipping nighttime BP pattern, potentially

placing them at higher risk for adverse CVD events. In this sample, almost half of subjects were considered ‘non-‘dippers’ ( 10% mean SBP dip from daytime to nighttime). The present findings also demonstrate that two behavioral interventions, exercise and stress management training, may augment nighttime BP dipping, which may help reduce the risk of adverse CVD events associated with blunted BP dipping.

Because sleep quality is directly related to the magnitude of nighttime BP dipping<sup>6, 24–26</sup>, one mechanism by which both the exercise and stress management training interventions may have enhanced BP dipping is by improving sleep quality. This possibility is supported by our finding that augmentation of nighttime BP dipping was achieved through post-intervention declines in nighttime BP, with little changing in daytime BP. No clinical trials have evaluated the effects of sleep medications on nighttime BP dipping. Nighttime dosing of melatonin, however, a hormone involved in diurnal regulation, appears to enhance nighttime BP dipping, possibly in part by improving sleep quality<sup>11</sup>. Stress is considered to be one of the most common causes of insomnia,<sup>27</sup> and exercise training may be an effective treatment for insomnia in a variety of patient populations.<sup>28–30</sup> As previously reported, participants in the present study who underwent stress management or exercise training showed a reduction in psychological distress,<sup>18</sup> which may have had a beneficial effects on their sleep quality.

These findings provide further evidence for the value of stress management and exercise training in improving cardiovascular health, and support previous reports that increased levels of physical activity may benefit BP dipping.<sup>14–16</sup> The mechanisms by which exercise may promote lower nighttime BP and augmented BP dipping have yet to be elucidated. Both exercise and stress management training have been shown to produce favorable changes in physiological regulatory systems, including improved vascular endothelial vasodilatory function.<sup>19</sup> Interestingly, impaired endothelial function has been linked both to nighttime hypertension and insomnia<sup>31, 32</sup>. Although exercise did not result in improved heart rate variability (HRV) measured during supine deep breathing, stress management training did improve HRV compared to Usual Care.<sup>19</sup> Reduced HRV is indicative of low parasympathetic activity, and has been associated with blunted nighttime BP dipping.<sup>33</sup> In contrast, reduced resting sympathetic activity is related to enhanced nighttime BP dipping.<sup>24, 26, 34</sup>

The present study has several limitations. These include a relatively small sample size for a clinical trial that was not powered specifically to examine the effects of exercise and stress management training on nighttime BP dipping. Due in part to the sample size limitation, the study was not designed to address mechanisms responsible for intervention effects on BP dipping. Nonetheless, our observations suggest that over the course of 16-weeks, two behavioral interventions, exercise and stress management training, can enhance nighttime BP dipping in CHD patients, who are both prone to exhibit blunted dipping and are at heightened risk of adverse clinical events.

Enhancing nocturnal blood pressure dipping by pharmacological chronotherapy has been shown to reduce subsequent cardiovascular events<sup>9</sup>. A small sub-study of the HOPE trial first showed that nighttime dosing of Ramipril reduced cardiovascular morbidity and

mortality in patients with peripheral arterial disease<sup>35</sup>. The MAPEC trial subsequently provided compelling evidence that in patients with hypertension, restoration of a normal nighttime “dipper” profile reduced the risk of CVD, stroke and new onset diabetes<sup>36</sup>. Nighttime dosing of antihypertensive medications typically augments BP dipping by lowering nighttime BP. Compared to usual care controls, this same phenomenon was evident for DBP dipping for the behavioral interventions. Because both exercise and stress management training improved other biomarkers of CVD risk, in addition to nighttime BP dipping, and also reduced psychological distress, these behavioral interventions also should reduce the risk for worse CHD outcomes<sup>18</sup>. For exercise training, the supportive evidence is already compelling, and recent evidence indicates that enhancing traditional cardiac rehabilitation with stress management training can further reduce risk of adverse clinical events in cardiac patients.<sup>37</sup>

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## ABBREVIATIONS

|             |                                      |
|-------------|--------------------------------------|
| <b>ABPM</b> | Ambulatory Blood Pressure Monitoring |
| <b>BDI</b>  | Beck Depression Inventory            |
| <b>CHD</b>  | Coronary Heart Disease               |
| <b>CVD</b>  | Cardiovascular Disease               |
| <b>DBP</b>  | Diastolic Blood Pressure             |
| <b>EX</b>   | Exercise (intervention)              |
| <b>ITT</b>  | Intent To Treat                      |
| <b>SBP</b>  | Systolic Blood Pressure              |
| <b>SM</b>   | Stress Management (intervention)     |
| <b>UC</b>   | Usual Care                           |

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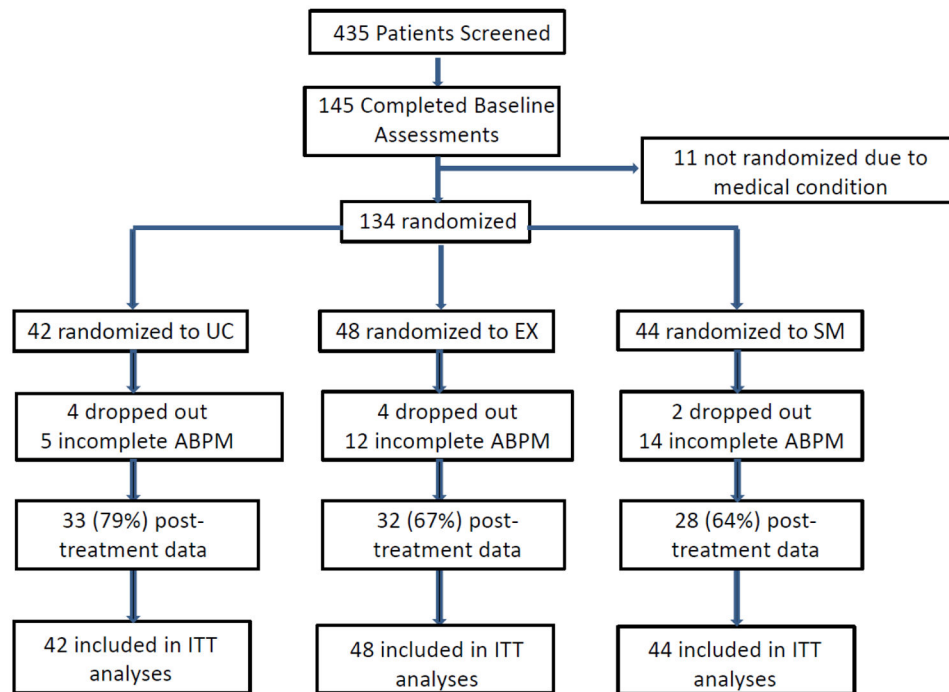
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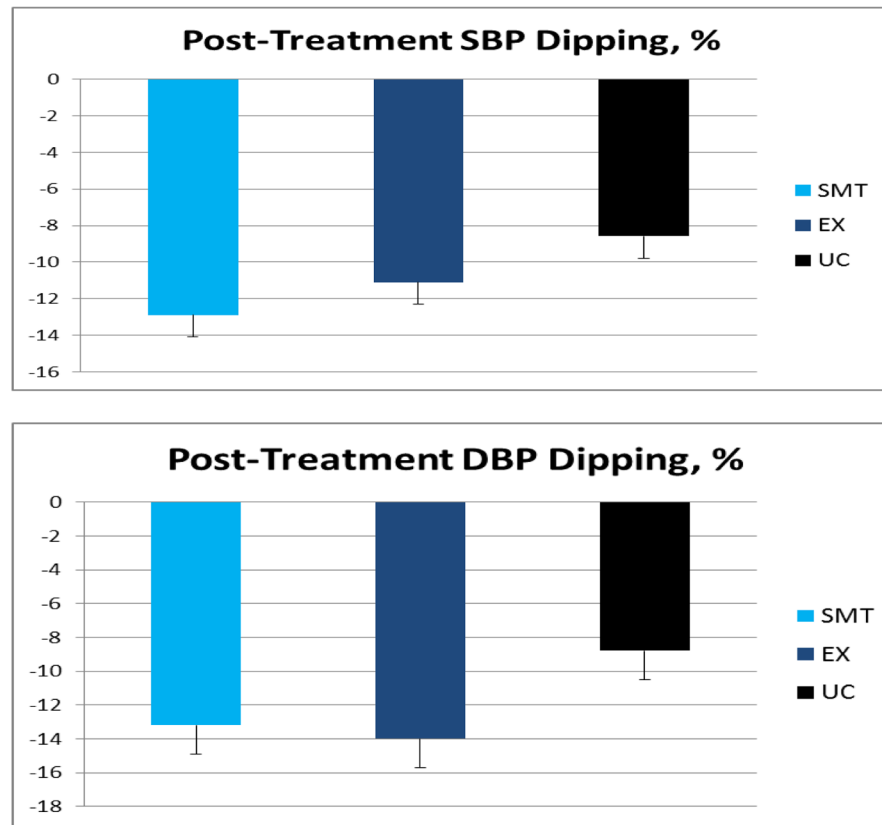
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**Figure 1.** Flow of participants from initial recruitment to end of treatment. SM = Stress Management training; EX = Exercise training; UC = Usual Care; ITT = intention-to-treat.



**Figure 2.** Post-intervention nighttime systolic (SBP) and diastolic (DBP) blood pressure dipping (%) following 16 weeks of Exercise (EX) training, Stress Management (SM) training, and Usual Care (UC).

**Table 1**

## Background Characteristics of the Study Sample

| Variable                    | UC (n = 42)  | EX (n = 48)  | SM (n = 44)  | Total Cohort (n = 134) |
|-----------------------------|--------------|--------------|--------------|------------------------|
| Age, yrs. (SD)              | 63 (9.0)     | 62 (10.5)    | 63 (11.5)    | 63 (10.3)              |
| Female N (%)                | 10 (24)      | 17 (35)      | 15 (34)      | 42 (31)                |
| Caucasian N (%)             | 32 (76)      | 36 (75)      | 35 (80)      | 103 (77)               |
| BMI, kg/m <sup>2</sup> (SD) | 29.8 (4.0)   | 29.9 (5.7)   | 29.0 (5.0)   | 29.8 (5.0)             |
| Clinic SBP, mmHg (SD)       | 137.1 (20.8) | 138.1 (20.0) | 135.2 (17.9) | 136.8 (19.5)           |
| Clinic DBP, mmHg (SD)       | 78.1 (9.7)   | 76.8 (6.5)   | 75.6 (9.7)   | 76.8 (8.7)             |
| Daytime SBP, mm Hg (SD)     | 127.9 (14.9) | 127.9 (12.3) | 128.5 (14.1) | 128.1 (13.6)           |
| Daytime DBP, mm Hg (SD)     | 74.6 (10.9)  | 73.8 (7.3)   | 74.1 (8.5)   | 74.1 (8.9)             |
| Nighttime SBP, mm Hg (SD)   | 115.2 (17.8) | 115.1 (12.9) | 117.3 (15.1) | 115.8 (15.2)           |
| Nighttime DBP, mm Hg (SD)   | 65.9 (12.1)  | 64.7 (8.9)   | 65.3 (8.9)   | 65.3 (9.8)             |
| SBP Dip, % (SD)             | 10.0 (7.7)   | 9.6 (7.8)    | 9.0 (7.6)    | 9.5 (7.7)              |
| DBP Dip, % (SD)             | 11.5 (8.8)   | 12.0 (9.1)   | 12.0 (8.6)   | 11.8 (8.8)             |

**Table 2**

Post intervention ambulatory blood pressures following 16 weeks of Exercise (EX) training, Stress Management (SM) training, and Usual Care (UC).

|                       | UC (N = 42) | EX (N = 48) | SM (N = 44) |
|-----------------------|-------------|-------------|-------------|
| Daytime SBP (mm Hg)   | 130 ± 2     | 131 ± 2     | 132 ± 2     |
| Nighttime SBP (mm Hg) | 119 ± 2     | 117 ± 2     | 115 ± 2     |
| SBP Dip (%)           | 9 ± 1       | 11 ± 1      | 13 ± 2      |
| Daytime DBP (mm Hg)   | 75 ± 1      | 74 ± 1      | 75 ± 1      |
| Nighttime DBP (mm Hg) | 68 ± 1      | 64 ± 1      | 65 ± 1      |
| DBP Dip (%)           | 9 ± 2       | 14 ± 2      | 13 ± 2      |